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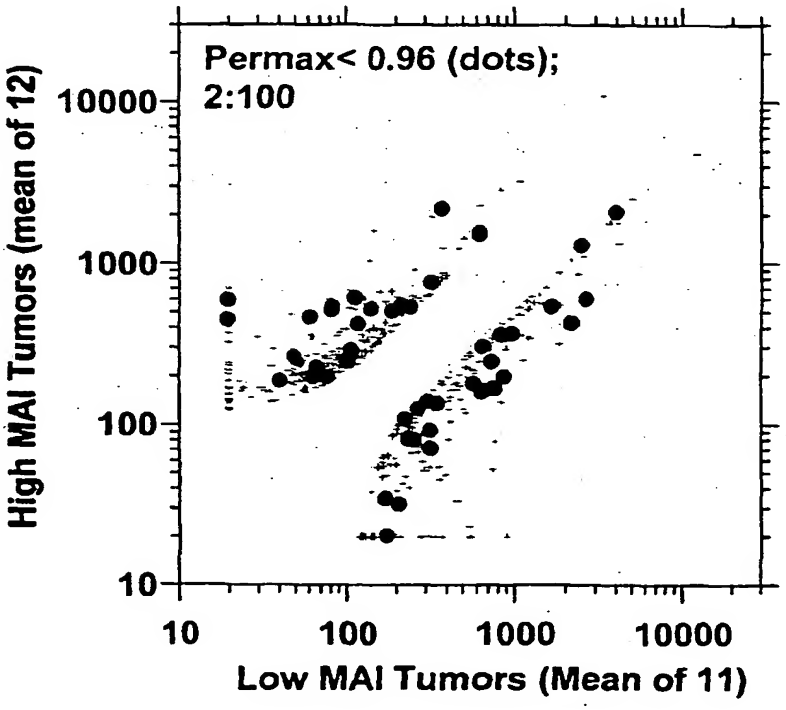
(54) Title: PROGNOSTIC CLASSIFICATION OF BREAST CANCER



(57) Abstract: The invention provides particular sets of genes that are expressed differentially in tumors characterized as high MAI or low MAI tumors. These sets of genes can be used to discriminate between high and low MAI tumors. Diagnostic assays for classification of tumors, prediction of tumor outcome, selecting and monitoring treatment regimens and monitoring tumor progression/regression are also provided.

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PROGNOSTIC CLASSIFICATION OF BREAST CANCER

Field of the Invention

The invention relates to nucleic acid microarray markers for cancer, particularly for breast cancer. The invention also relates to methods for diagnosing cancer as well as optimizing cancer treatment strategies.

Background of the Invention

Breast cancer is a malignant proliferation of epithelial cells lining the ducts or lobules of the breast (Harrison's Principles of Internal Medicine 1998). Although much progress has been made toward understanding the biological basis of cancer and in its diagnosis and treatment, it is still one of the leading causes of death in the United States. Inherent difficulties in the diagnosis and treatment of cancer include among other things, the existence of many different subgroups of cancer and the concomitant variation in appropriate treatment strategies to maximize the likelihood of positive patient outcome.

The traditional method of breast cancer diagnosis and staging is through the use of biopsy examination. Once a diagnosis is made, the options for treating breast cancer are assessed with respect to the needs of the patient. These options traditionally include surgical intervention, chemotherapy, radiotherapy, and adjuvant systemic therapies. Surgical therapy may be lumpectomy or more extensive mastectomy. Adjuvants may include but are not limited to chemotherapy, radiotherapy, and endocrine therapies such as castration; administration of LHRH agonists, antiestrogens, such as tamoxifen, high-dose progestogens; adrenalectomy; and/or aromatase inhibitors (Harrison's Principles of Internal Medicine 1998).

Of key importance in the treatment of breast cancer is the selection and implementation of an appropriate combination of therapeutic approaches. For example, depending on a breast cancer patient's prognosis, therapy may include surgical intervention in combination with adjuvant therapy or it may only include surgical intervention. In addition, for some patients pretreatment with chemotherapy or radiotherapy is utilized prior to surgical intervention, but in other patients adjuvant therapies are used following surgical intervention.

It is difficult to predict from standard clinical and pathologic features the clinical course of early stage breast cancer, particularly lymph node-negative tumors in

premenopausal patients. Current practice in the United States is to offer systemic chemotherapy to most of these women. Because the majority of these women would have good outcome even without chemotherapy, the rate of "over-treatment" is high. Chemotherapy itself carries a 1% mortality rate. Therefore, unnecessary deaths could be avoided if it were possible to subdivide these patients into high and low risk subgroups, and only undertake adjunctive treatment for those judged to be high risk.

Selection of a suitable treatment regimen for breast cancer is based on the subgroup of cancer. Current strategies used to make therapeutic decisions in the management of patients with breast cancer are based on several factors including hormone receptor status, her-2/neu staining, flow cytometry, and the mitotic activity index (MAI). The MAI is a widely utilized predictor of outcome in cancers, particularly in invasive breast cancer. The definition of the MAI is "the total number of mitoses counted in 10 consecutive high-power fields (objective, x40; numeric aperture, .75; field diameter, 450 microns), in the most cellular area at the periphery of the tumor, with the subjectively highest mitotic activity" (Jannink et al., 1995). For the procedure, hematoxylin-eosin stained sections of breast cancer tumor are assessed for the total number of mitotic figures in ten consecutive high-power fields and based on these numbers the breast cancer is assigned to either good outcome (MAI<10) or poor outcome (MAI>10). MAI classification correlates to standard parameters such as death, recurrence, and metastases, which are known to those of ordinary skill in the art to predict clinical outcome.

Determination of appropriate treatment for an individual cancer patient is complex with a wide variety of treatments and possible treatment combinations. For example, chemotherapy is a common method of cancer treatment, with more than 50 different chemotherapeutic agents available. These therapeutic agents can be used in a wide range of dosages both singly and in combinational therapies with other chemotherapeutic agents, surgery, and/or radiotherapy.

The available methods for designing strategies for treating breast cancer patients are complex, time consuming, and inexact. The wide range of cancer subgroups and variations in disease progression limit the predictive ability of the healthcare professional. In addition, continuing development of novel treatment strategies and therapeutics will result in the addition of more variables to the already complex decision-making process involving matching the cancer patient with a treatment regimen that is appropriate and optimized for the cancer stage, extent of infiltration, tumor growth rate, and other factors central to the

individual patient's prognosis. Because of the critical importance of selecting appropriate treatment regimens for breast cancer patients, the development of guidelines for treatment selection is of key interest to those in the medical community and their patients. Thus, there presently is a need for objective, reproducible, and sensitive methods for predicting breast cancer patient outcome and selecting optimal treatment regimens.

Summary of the Invention

It now has been discovered that particular sets of genes are expressed differentially in tumors characterized as high MAI or low MAI tumors. These sets of genes can be used to discriminate between high and low MAI tumors. Accordingly, diagnostic assays for classification of tumors, prediction of tumor outcome, selecting and monitoring treatment regimens and monitoring tumor progression/regression can now be based on the expression of sets of genes.

According to one aspect of the invention, methods for diagnosing breast cancer in a subject suspected of having breast cancer are provided. The methods include obtaining from the subject a breast tissue sample and determining the expression of a set of nucleic acid molecules or expression products thereof in the breast tissue sample. The set of nucleic acid molecules includes at least two nucleic acid molecules selected from the group consisting of SEQ ID NOs:1-51. In preferred embodiments, the breast tissue sample suspected of being cancerous.

In some embodiments the set of nucleic acid molecules includes more than 2 and up to all of the nucleic acid molecules set forth as SEQ ID NOs:1-51, and any number of nucleic acid sequences between these two numbers. For example, in certain embodiments the set includes at least 3, 4, 5, 10, 15, 20, 30, 40 or more nucleic acid molecules of the nucleic acid molecules set forth as SEQ ID NOs:1-51.

In other embodiments, the method further includes determining the expression of the set of nucleic acid molecules or expression products thereof in a non-cancerous breast tissue sample, and comparing the expression of the set of nucleic acid molecules or expression products thereof in the breast tissue sample suspected of being cancerous and the non-cancerous breast tissue sample.

According to another aspect of the invention, methods for identifying a set of nucleic acid markers or expression products thereof are provided. The methods are effective for determining the prognosis of cancer. The methods include obtaining a plurality of tumor

tissue samples from a plurality of subjects afflicted with cancer, classifying the plurality of tumor tissue samples according to mitotic activity index (MAI) into high MAI and low MAI groups and determining differences in the expression of a plurality of nucleic acid molecules or expression products thereof in the tumor tissue samples. The methods further include selecting as a set of nucleic acid markers the nucleic acid molecules or expression products thereof which are differentially expressed in the high MAI and the low MAI groups. The set of nucleic acid markers or expression products thereof effective for determining poor prognosis of cancer includes one or more nucleic acid molecules or expression products thereof which are preferentially expressed in high MAI tumor tissue samples, and wherein the set of nucleic acid markers or expression products thereof effective for determining good prognosis of cancer comprises one or more nucleic acid molecules or expression products thereof which are preferentially expressed in low MAI tumor tissue samples. In preferred embodiments, the cancer is breast cancer.

According to still another aspect of the invention, methods for selecting a course of treatment of a subject having or suspected of having cancer are provided. The methods include obtaining from the subject a tissue sample suspected of being cancerous, determining the expression of a set of nucleic acid markers or expression products thereof which are differentially expressed in high MAI tumor tissue samples to determine the MAI of the tissue sample of the subject, and selecting a course of treatment appropriate to the cancer of the subject.

In preferred embodiments the cancer is breast cancer, and in some of these embodiments the methods include determining the expression of a set of nucleic acid markers that are differentially expressed in low MAI breast tumor tissue samples.

According to yet another aspect of the invention, methods for evaluating treatment of cancer are provided. The methods include obtaining a first determination of the expression of a set of nucleic acid molecules or expression products thereof, which are differentially expressed in high MAI tumor tissue samples to determine the MAI of the tissue sample from a subject undergoing treatment for cancer, and obtaining a second determination of the expression of a set of nucleic acid molecules or expression products thereof, which are differentially expressed in high MAI tumor tissue samples to determine the MAI of the second tissue sample from the subject after obtaining the first determination. The methods also include comparing the first determination of expression to the second determination of expression as an indication of evaluation of the treatment.

In preferred embodiments the cancer is breast cancer, and in some of these embodiments the methods include determining the expression of a set of nucleic acid markers that are differentially expressed in low MAI breast tumor tissue samples.

The invention in another aspect provides solid-phase nucleic acid molecule arrays. The arrays have a cancer gene marker set that consists essentially of at least two and as many as all of the nucleic acid molecules set forth as SEQ ID NOs:1-51 fixed to a solid substrate. The set of nucleic acid markers can include any number of nucleic acid sequences between these two numbers, selected from SEQ ID NOs:1-51. For example, in certain embodiments the set includes at least 3, 4, 5, 10, 15, 20, 30, 40 or more nucleic acid molecules of the nucleic acid molecules set forth as SEQ ID NOs:1-51. In some embodiments, the solid-phase nucleic acid molecule array also includes at least one control nucleic acid molecule.

In certain embodiments, the solid substrate includes a material selected from the group consisting of glass, silica, aluminosilicates, borosilicates, metal oxides such as alumina and nickel oxide, various clays, nitrocellulose, or nylon. Preferably the substrate is glass.

In other embodiments, the nucleic acid molecules are fixed to the solid substrate by covalent bonding.

According to yet another aspect of the invention, protein microarrays are provided. The protein microarrays include antibodies or antigen-binding fragments thereof, that specifically bind at least two different polypeptides selected from the group consisting of SEQ ID NOs:52-102, fixed to a solid substrate. In some embodiments, the microarray comprises antibodies or antigen-binding fragments thereof, that bind specifically to least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50 or 51 different polypeptides selected from the group consisting of SEQ ID NOs:52-102. In certain embodiments, the microarray also includes an antibody or antigen-binding fragment thereof, that binds specifically to a cancer-associated polypeptide other than those selected from the group consisting of SEQ ID NOs:52-102, preferably a breast cancer associated polypeptide. In some embodiments, the protein microarray also includes at least one control polypeptide molecule. In further embodiments, the antibodies are monoclonal or polyclonal antibodies. In other embodiments, the antibodies are chimeric, human, or humanized antibodies. In some embodiments, the antibodies are single chain antibodies. In still other embodiments, the antigen-binding fragments are $F(ab')_2$, Fab, Fd, or Fv fragments.

In a further aspect of the invention, methods for identifying lead compounds for a pharmacological agent useful in the treatment of breast cancer are provided. The methods include contacting a breast cancer cell or tissue with a candidate pharmacological agent, and determining the expression of a set of nucleic acid molecules in the breast cancer cell or tissue sample under conditions which, in the absence of the candidate pharmacological agent, permit a first amount of expression of the set of nucleic acid molecules. The set of nucleic acid molecules includes at least two and as many as all of the nucleic acid molecules set forth as SEQ ID NOs:1-51. The methods also include detecting a test amount of the expression of the set of nucleic acid molecules, wherein a decrease in the test amount of expression in the presence of the candidate pharmacological agent relative to the first amount of expression indicates that the candidate pharmacological agent is a lead compound for a pharmacological agent which is useful in the treatment of breast cancer. In preferred embodiments, the set of nucleic acid molecules is differentially expressed in high MAI breast tumor tissue samples.

In some embodiments of any of the foregoing methods and products, the differences in the expression of a the nucleic acid molecules are determined by nucleic acid hybridization or nucleic acid amplification methods. Preferably the nucleic acid hybridization is performed using a solid-phase nucleic acid molecule array. In other embodiments, the differences in the expression of the nucleic acid molecules are determined by protein expression analysis, preferably SELDI mass spectroscopy.

These and other aspects of the invention will be described in greater detail below.

Brief Description of the Drawings

Figure 1 is a scatterplot of gene expression level in low risk (x axis) and high risk (y axis) breast cancers. 422 genes whose mean expression between groups differs at least 2-fold and by 100 expression units are shown as small crosses. The top 51 t-test ranked genes with Permax 0.96 are indicated as solid circles, and appear in Table 1.

Detailed Description of the Invention

The invention described herein relates to the identification of a set of genes expressed in breast cancer tissue that are predictive of the clinical outcome of the cancer. Changes in cell phenotype in cancer are often the result of one or more changes in the genome expression of the cell. Some genes are expressed in tumor cells, and not in normal cells. In addition, different genes are expressed in different subgroups of breast cancers, which have different

prognoses and require different treatment regimens to optimize patient outcome. The differential expression of breast cancer genes can be examined by the assessment of nucleic acid or protein expression in the breast cancer tissue.

The genes were identified by screening nucleic acid molecules isolated from various breast cancer samples for expression of the genes present on a high-density nucleic acid microarray. The breast cancer samples were categorized with respect to their mitotic activity index (MAI) and the MAI was correlated to gene expression to identify those genes differentially expressed between low and high-MAI breast cancer tissue. The MAI has been shown to correlate with the outcome of the cancer as defined by tumor metastasis, tumor recurrence or mortality. Accordingly the genes identified permit, *inter alia*, rapid screening of cancer samples by nucleic acid microarray hybridization or protein expression technology to determine the expression of the specific genes and thereby to predict the outcome of the cancer. Such screening is beneficial, for example, in selecting the course of treatment to provide to the cancer patient, and to monitor the efficacy of a treatment.

The invention differs from traditional breast cancer diagnostic and classification techniques including MAI, hormone receptor expression and her-2/neu expression, with respect to the speed, simplicity, and reproducibility of the cancer diagnostic assay. The invention also presents targets for drug development because it identifies genes that are differentially expressed in poor outcome breast tumors, which can be utilized in the development of drugs to treat such tumors, e.g., by reducing expression of the genes or reducing activity of proteins encoded by the genes.

The invention moves beyond the use of the MAI and simplifies prognosis determination by providing an identified set of genes whose expression in breast cancers predicts poor clinical outcome as defined by tumor metastasis, recurrence, or death. In the invention, the MAI was used in conjunction with RNA expression phenotyping performed using high density microarrays generated from quantitative expression data on over 5000 (estimated 5800) genes, which have been analyzed to identify 51 specific probe sets (genes) with divergent expression between MAI groups. The expression gene set has multifold uses including, but not limited to, the following examples. The expression gene set may be used as a prognostic tool for breast cancer patients, to make possible more finely tuned diagnosis of breast cancer and allow healthcare professionals to tailor treatment to individual patients' needs. The invention can also assess the efficacy of breast cancer treatment by determining progression or regression of breast cancer in patients before, during, and after breast cancer

treatment. Another utility of the expression gene set is in the biotechnology and pharmaceutical industries' research on disease pathway discovery for therapeutic targeting. The invention can identify alterations in gene expression in breast cancer and can also be used to uncover and test candidate pharmaceutical agents to treat breast cancer.

Although the invention is described primarily with respect to breast cancer, one of ordinary skill in the art will appreciate that the invention also is useful for diagnosis and prognosis determination of cancers that can be classified into subgroups for prognosis of the cancer based on MAI. For example, MAI has been used successfully in the classification of malignant melanoma, ovarian cancer, bladder cancer, and prostatic adenocarcinoma. Thus, the methods and products of the invention also are applicable to non-breast cancers that can be classified by MAI.

The invention may also encompass cancers other than breast cancer, including but not limited to: biliary tract cancer; bladder cancer; brain cancer including glioblastomas and medulloblastomas; cervical cancer; choriocarcinoma; colon cancer; endometrial cancer; esophageal cancer; gastric cancer; hematological neoplasms including acute lymphocytic and myelogenous leukemia; multiple myeloma; AIDS-associated leukemias and adult T-cell leukemia lymphoma; intraepithelial neoplasms including Bowen's disease and Paget's disease; liver cancer; lung cancer; lymphomas including Hodgkin's disease and lymphocytic lymphomas; neuroblastomas; oral cancer including squamous cell carcinoma; ovarian cancer including those arising from epithelial cells, stromal cells, germ cells and mesenchymal cells; pancreatic cancer; prostate cancer; rectal cancer; sarcomas including leiomyosarcoma, rhabdomyosarcoma, liposarcoma, fibrosarcoma, and osteosarcoma; skin cancer including melanoma, Kaposi's sarcoma, basocellular cancer, and squamous cell cancer; testicular cancer including germinal tumors such as seminoma, non-seminoma (teratomas, choriocarcinomas), stromal tumors, and germ cell tumors; thyroid cancer including thyroid adenocarcinoma and medullar carcinoma; and renal cancer including adenocarcinoma and Wilms tumor.

As used herein, a subject is a human, non-human primate, cow, horse, pig, sheep, goat, dog, cat or rodent. In all embodiments human subjects are preferred. Preferably the subject is a human either suspected of having breast cancer, or having been diagnosed with breast cancer. In a preferred embodiment of the invention the cancer is pre-menopausal, lymph node–negative breast cancer. Methods for identifying subjects suspected of having breast cancer may include manual examination, biopsy, subject's family medical history,

subject's medical history, or a number of imaging technologies such as mammography, magnetic resonance imaging, magnetic resonance spectroscopy, or positron emission tomography. Diagnostic methods for breast cancer and the clinical delineation of breast cancer diagnoses are well-known to those of skill in the medical arts.

As used herein, breast tissue sample is tissue obtained from a breast tissue biopsy using methods well-known to those of ordinary skill in the related medical arts. The phrase "suspected of being cancerous" as used herein means a breast cancer tissue sample believed by one of ordinary skill in the medical arts to contain cancerous cells. Methods for obtaining the sample from the biopsy include gross apportioning of a mass, microdissection, laser-based microdissection, or other art-known cell-separation methods.

Because of the variability of the cell types in diseased-tissue biopsy material, and the variability in sensitivity of the diagnostic methods used, the sample size required for analysis may range from 1, 10, 50, 100, 200, 300, 500, 1000, 5000, 10,000, to 50,000 or more cells. The appropriate sample size may be determined based on the cellular composition and condition of the biopsy and the standard preparative steps for this determination and subsequent isolation of the nucleic acid for use in the invention are well known to one of ordinary skill in the art. An example of this, although not intended to be limiting, is that in some instances a sample from the biopsy may be sufficient for assessment of RNA expression without amplification, but in other instances the lack of suitable cells in a small biopsy region may require use of RNA conversion and/or amplification methods or other methods to enhance resolution of the nucleic acid molecules. Such methods, which allow use of limited biopsy materials, are well known to those of ordinary skill in the art and include, but are not limited to: direct RNA amplification, reverse transcription of RNA to cDNA, amplification of cDNA, or the generation of radio-labeled nucleic acids.

As used herein, the phrase "determining the expression of a set of nucleic acid molecules in the breast tissue" means identifying RNA transcripts in the tissue sample by analysis of nucleic acid or protein expression in the tissue sample. As used herein, "set" refers to a group of nucleic acid molecules that include 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, or 51 different nucleic acid sequences from the group of nucleic acid sequences numbered 1 through 51 in Table 1 (SEQ ID Nos: 1-51).

The expression of the set of nucleic acid molecules in the sample from the breast cancer patient can be compared to the expression of the set of nucleic acid molecules in a

sample of breast tissue that is non-cancerous. As used herein, non-cancerous breast tissue means tissue determined by one of ordinary skill in the medical art to have no evidence of breast cancer based on standard diagnostic methods including, but not limited to, histologic staining and microscopic analysis.

Nucleic acid markers for cancer are nucleic acid molecules that by their presence or absence indicate the presence of absence of breast cancer. In tissue, certain nucleic acid molecules are expressed at different levels depending on whether tissue is non-cancerous or cancerous. In cancerous tissue, nucleic acid molecule expression may be correlated with MAI prognostic analysis. As described herein, breast cancer nucleic acid markers were identified by evaluating the nucleic acid molecules present in breast tumor tissue samples and comparing expression levels of the nucleic acid molecules with MAI levels determined for the tissues. An aspect of the invention is that different nucleic acid molecules are expressed in breast cancers with different MAI levels (i.e., high MAI versus low MAI) and these expression variations are identifiable by nucleic acid expression analysis, such as microarray analysis or protein expression analysis. Some nucleic acids are more likely to be, in other words, are preferentially expressed in cancers with high MAI levels and other nucleic acids are preferentially expressed in cancers with low MAI levels. According to the invention, the correlation between the preferential expression of nucleic acid markers and MAI classification allows expression of nucleic acid markers to be used to directly categorize breast cancers as low MAI or high MAI. Thus, nucleic acid expression-based categorization of breast cancer (by measurement of nucleic acid or protein expression) as low or high MAI may be used by one of ordinary skill in the medical arts to select an appropriate treatment regimen based on a patient's specific breast cancer prognosis.

Hybridization methods for nucleic acids are well known to those of ordinary skill in the art (see, e.g. *Molecular Cloning: A Laboratory Manual*, J. Sambrook, et al., eds., Second Edition, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York, 1989, or *Current Protocols in Molecular Biology*, F.M. Ausubel, et al., eds., John Wiley & Sons, Inc., New York). The nucleic acid molecules from a breast cancer tissue sample hybridize under stringent conditions to nucleic acid markers expressed in breast cancer. In one embodiment the markers are sets of two or more of the nucleic acid molecules as set forth in SEQ ID NOs: 1 through 51.

The breast cancer nucleic acid markers disclosed herein are known genes and fragments thereof. It may be desirable to identify variants of those genes, such as allelic

variants or single nucleotide polymorphisms (SNPs) in tissues. Accordingly, methods for identifying breast cancer nucleic acid markers, including variants of the disclosed full-length cDNAs, genomic DNAs, and SNPs are also included in the invention. The methods include contacting a nucleic acid sample (such as a cDNA library, genomic library, genomic DNA isolate, etc.) with a nucleic acid probe or primer derived from one of SEQ ID NOs:1 through 51. The nucleic acid sample and the probe or primer hybridize to complementary nucleotide sequences of nucleic acids in the sample, if any are present, allowing detection of nucleic acids related to SEQ ID NOs: 1-51. Preferably the probe or primer is detectably labeled. The specific conditions, reagents, and the like can be selected by one of ordinary skill in the art to selectively identify nucleic acids related to sets of two or more of SEQ ID NOs:1 through 51. The isolated nucleic acid molecule can be sequenced according to standard procedures.

In addition to native nucleic acid markers (SEQ ID NOs:1-51), the invention also includes degenerate nucleic acids that include alternative codons to those present in the native materials. For example, serine residues are encoded by the codons TCA, AGT, TCC, TCG, TCT, and AGC. Each of the six codons is equivalent for the purposes of encoding a serine residue. Similarly, nucleotide sequence triplets that encode other amino acid residues include, but are not limited to: CCA, CCC, CCG, and CCT (proline codons); CGA, CGC, CGG, CGT, AGA, and AGG (arginine codons); ACA, ACC, ACG, and ACT (threonine codons); AAC and AAT (asparagine codons); and ATA, ATC, and ATT (isoleucine codons). Other amino acid residues may be encoded similarly by multiple nucleotide sequences. Thus, the invention embraces degenerate nucleic acids that differ from the biologically isolated nucleic acids in codon sequence due to the degeneracy of the genetic code.

The invention also provides modified nucleic acid molecules, which include additions, substitutions, and deletions of one or more nucleotides such as the allelic variants and SNPs described above. In preferred embodiments, these modified nucleic acid molecules and/or the polypeptides they encode retain at least one activity or function of the unmodified nucleic acid molecule and/or the polypeptides, such as hybridization, antibody binding, etc. In certain embodiments, the modified nucleic acid molecules encode modified polypeptides, preferably polypeptides having conservative amino acid substitutions . As used herein, a "conservative amino acid substitution" refers to an amino acid substitution which does not alter the relative charge or size characteristics of the protein in which the amino acid substitution is made. Conservative substitutions of amino acids include substitutions made amongst amino acids within the following groups: (a) M, I, L, V; (b) F, Y, W; (c) K, R, H;

(d) A, G; (e) S, T; (f) Q, N; and (g) E, D. The modified nucleic acid molecules are structurally related to the unmodified nucleic acid molecules and in preferred embodiments are sufficiently structurally related to the unmodified nucleic acid molecules so that the modified and unmodified nucleic acid molecules hybridize under stringent conditions known to one of skill in the art.

For example, modified nucleic acid molecules that encode polypeptides having single amino acid changes can be prepared for use in the methods and products disclosed herein. Each of these nucleic acid molecules can have one, two, or three nucleotide substitutions exclusive of nucleotide changes corresponding to the degeneracy of the genetic code as described herein. Likewise, modified nucleic acid molecules that encode polypeptides having two amino acid changes can be prepared, which have, e.g., 2-6 nucleotide changes. Numerous modified nucleic acid molecules like these will be readily envisioned by one of skill in the art, including for example, substitutions of nucleotides in codons encoding amino acids 2 and 3, 2 and 4, 2 and 5, 2 and 6, and so on. In the foregoing example, each combination of two amino acids is included in the set of modified nucleic acid molecules, as well as all nucleotide substitutions which code for the amino acid substitutions. Additional nucleic acid molecules that encode polypeptides having additional substitutions (i.e., 3 or more), additions or deletions [e.g., by introduction of a stop codon or a splice site(s)] also can be prepared and are embraced by the invention as readily envisioned by one of ordinary skill in the art. Any of the foregoing nucleic acids can be tested by routine experimentation for retention of structural relation to or activity similar to the nucleic acids disclosed herein.

In the invention, standard hybridization techniques of microarray technology are utilized to assess patterns of nucleic acid expression and identify nucleic acid marker expression. Microarray technology, which is also known by other names including: DNA chip technology, gene chip technology, and solid-phase nucleic acid array technology, is well known to those of ordinary skill in the art and is based on, but not limited to, obtaining an array of identified nucleic acid probes on a fixed substrate, labeling target molecules with reporter molecules (e.g., radioactive, chemiluminescent, or fluorescent tags such as fluorescein, Cye3-dUTP, or Cye5-dUTP), hybridizing target nucleic acids to the probes, and evaluating target-probe hybridization. A probe with a nucleic acid sequence that perfectly matches the target sequence will, in general, result in detection of a stronger reporter-molecule signal than will probes with less perfect matches. Many components and techniques utilized in nucleic acid microarray technology are presented in *The Chipping*

Forecast, Nature Genetics, Vol.21, Jan 1999, the entire contents of which is incorporated by reference herein.

According to the present invention, microarray substrates may include but are not limited to glass, silica, aluminosilicates, borosilicates, metal oxides such as alumina and nickel oxide, various clays, nitrocellulose, or nylon. In all embodiments a glass substrate is preferred. According to the invention, probes are selected from the group of nucleic acids including, but not limited to: DNA, genomic DNA, cDNA, and oligonucleotides; and may be natural or synthetic. Oligonucleotide probes preferably are 20 to 25-mer oligonucleotides and DNA/cDNA probes preferably are 500 to 5000 bases in length, although other lengths may be used. Appropriate probe length may be determined by one of ordinary skill in the art by following art-known procedures. In one embodiment, preferred probes are sets of two or more of the nucleic acid molecules set forth as SEQ ID NO: 1 through 51 (see also Table 1). Probes may be purified to remove contaminants using standard methods known to those of ordinary skill in the art such as gel filtration or precipitation.

In one embodiment, the microarray substrate may be coated with a compound to enhance synthesis of the probe on the substrate. Such compounds include, but are not limited to, oligoethylene glycols. In another embodiment, coupling agents or groups on the substrate can be used to covalently link the first nucleotide or olignucleotide to the substrate. These agents or groups may include, but are not limited to: amino, hydroxy, bromo, and carboxy groups. These reactive groups are preferably attached to the substrate through a hydrocarbyl radical such as an alkylene or phenylene divalent radical, one valence position occupied by the chain bonding and the remaining attached to the reactive groups. These hydrocarbyl groups may contain up to about ten carbon atoms, preferably up to about six carbon atoms. Alkylene radicals are usually preferred containing two to four carbon atoms in the principal chain. These and additional details of the process are disclosed, for example, in U.S. Patent 4,458,066, which is incorporated by reference in its entirety.

In one embodiment, probes are synthesized directly on the substrate in a predetermined grid pattern using methods such as light-directed chemical synthesis, photochemical deprotection, or delivery of nucleotide precursors to the substrate and subsequent probe production.

In another embodiment, the substrate may be coated with a compound to enhance binding of the probe to the substrate. Such compounds include, but are not limited to: polylysine, amino silanes, amino-reactive silanes (Chipping Forecast, 1999) or chromium

(Gwynne and Page, 2000). In this embodiment, presynthesized probes are applied to the substrate in a precise, predetermined volume and grid pattern, utilizing a computer-controlled robot to apply probe to the substrate in a contact-printing manner or in a non-contact manner such as ink jet or piezo-electric delivery. Probes may be covalently linked to the substrate with methods that include, but are not limited to, UV-irradiation. In another embodiment probes are linked to the substrate with heat.

Targets are nucleic acids selected from the group, including but not limited to: DNA, genomic DNA, cDNA, RNA, mRNA and may be natural or synthetic. In all embodiments, nucleic acid molecules from human breast tissue are preferred. The tissue may be obtained from a subject or may be grown in culture (e.g. from a breast cancer cell line).

In embodiments of the invention one or more control nucleic acid molecules are attached to the substrate. Preferably, control nucleic acid molecules allow determination of factors including but not limited to: nucleic acid quality and binding characteristics; reagent quality and effectiveness; hybridization success; and analysis thresholds and success. Control nucleic acids may include but are not limited to expression products of genes such as housekeeping genes or fragments thereof.

To select a set of tumor markers, the expression data generated by, for example, microarray analysis of gene expression, is preferably analyzed to determine which genes in different groups of cancer tissues are significantly differentially expressed. In the methods disclosed herein, the significance of gene expression was determined using Permax computer software, although any standard statistical package that can discriminate significant differences in expression may be used. Permax performs permutation 2-sample t-tests on large arrays of data. For high dimensional vectors of observations, the Permax software computes t-statistics for each attribute, and assesses significance using the permutation distribution of the maximum and minimum overall attributes. The main use is to determine the attributes (genes) that are the most different between two groups (e.g., high MAI tissues versus low MAI tissues), measuring "most different" using the value of the t-statistics, and their significance levels.

In one embodiment of the invention, expression of nucleic acid markers is used to select clinical treatment paradigms for breast cancer. Treatment options, as described herein, may include but are not limited to: chemotherapy, radiotherapy, adjuvant therapy, or any combination of the aforementioned methods. Aspects of treatment that may vary include, but are not limited to: dosages, timing of administration, or duration or therapy; and may or may

not be combined with other treatments, which may also vary in dosage, timing, or duration. Another treatment for breast cancer is surgery, which can be utilized either alone or in combination with any of the aforementioned treatment methods. One of ordinary skill in the medical arts may determine an appropriate treatment paradigm based on evaluation of differential expression of sets of two or more of the nucleic acid targets SEQ ID NOs:1-51. Cancers that express markers that are indicative of a more aggressive cancer or poor prognosis may be treated with more aggressive therapies.

Progression or regression of breast cancer is determined by comparison of two or more different breast cancer tissue samples taken at two or more different times from a subject. For example, progression or regression may be evaluated by assessments of expression of sets of two or more of the nucleic acid targets, including but not limited to SEQ ID NOs:1-51, in a breast cancer tissue sample from a subject before, during, and following treatment for breast cancer.

In another embodiment, novel pharmacological agents useful in the treatment of breast cancer can be identified by assessing variations in the expression of sets of two or more breast cancer nucleic acid markers, from among SEQ ID NOs:1-51, prior to and after contacting breast cancer cells or tissues with candidate pharmacological agents for the treatment of breast cancer. The cells may be grown in culture (e.g. from a breast cancer cell line), or may be obtained from a subject, (e.g. in a clinical trial of candidate pharmaceutical agents to treat breast cancer). Alterations in expression of two or more sets of breast cancer nucleic acid markers, from among SEQ ID NOs:1-51, in breast cancer cells or tissues tested before and after contact with a candidate pharmacological agent to treat breast cancer, indicate progression, regression, or stasis of the breast cancer thereby indicating efficacy of candidate agents and concomitant identification of lead compounds for therapeutic use in breast cancer.

The invention further provides efficient methods of identifying pharmacological agents or lead compounds for agents active at the level of breast cancer cellular function. Generally, the screening methods involve assaying for compounds that beneficially alter breast cancer nucleic acid molecule expression. Such methods are adaptable to automated, high throughput screening of compounds.

The assay mixture comprises a candidate pharmacological agent. Typically, a plurality of assay mixtures are run in parallel with different agent concentrations to obtain a different response to the various concentrations. Typically, one of these concentrations

serves as a negative control, i.e., at zero concentration of agent or at a concentration of agent below the limits of assay detection. Candidate agents encompass numerous chemical classes, although typically they are organic compounds. Preferably, the candidate pharmacological agents are small organic compounds, i.e., those having a molecular weight of more than 50 yet less than about 2500, preferably less than about 1000 and, more preferably, less than about 500. Candidate agents comprise functional chemical groups necessary for structural interactions with polypeptides and/or nucleic acids, and typically include at least an amine, carbonyl, hydroxyl or carboxyl group, preferably at least two of the functional chemical groups and more preferably at least three of the functional chemical groups. The candidate agents can comprise cyclic carbon or heterocyclic structure and/or aromatic or polyaromatic structures substituted with one or more of the above-identified functional groups. Candidate agents also can be biomolecules such as peptides, saccharides, fatty acids, sterols, isoprenoids, purines, pyrimidines, derivatives or structural analogs of the above, or combinations thereof and the like. Where the agent is a nucleic acid, the agent typically is a DNA or RNA molecule, although modified nucleic acids as defined herein are also contemplated.

Candidate agents are obtained from a wide variety of sources including libraries of synthetic or natural compounds. For example, numerous means are available for random and directed synthesis of a wide variety of organic compounds and biomolecules, including expression of randomized oligonucleotides, synthetic organic combinatorial libraries, phage display libraries of random peptides, and the like. Alternatively, libraries of natural compounds in the form of bacterial, fungal, plant and animal extracts are available or readily produced. Additionally, natural and synthetically produced libraries and compounds can be readily be modified through conventional chemical, physical, and biochemical means. Further, known pharmacological agents may be subjected to directed or random chemical modifications such as acylation, alkylation, esterification, amidification, etc. to produce structural analogs of the agents.

A variety of other reagents also can be included in the mixture. These include reagents such as salts, buffers, neutral proteins (e.g., albumin), detergents, etc. which may be used to facilitate optimal protein-protein and/or protein-nucleic acid binding. Such a reagent may also reduce non-specific or background interactions of the reaction components. Other reagents that improve the efficiency of the assay such as protease, inhibitors, nuclease inhibitors, antimicrobial agents, and the like may also be used.

The mixture of the foregoing assay materials is incubated under conditions whereby, the anti-breast cancer candidate agent specifically binds the cellular binding target, a portion thereof or analog thereof. The order of addition of components, incubation temperature, time of incubation, and other parameters of the assay may be readily determined. Such experimentation merely involves optimization of the assay parameters, not the fundamental composition of the assay. Incubation temperatures typically are between 4°C and 40°C. Incubation times preferably are minimized to facilitate rapid, high throughput screening, and typically are between 0.1 and 10 hours.

After incubation, the presence or absence of specific binding between the anti-breast cancer candidate agent and one or more binding targets is detected by any convenient method available to the user. For cell-free binding type assays, a separation step is often used to separate bound from unbound components. The separation step may be accomplished in a variety of ways. Conveniently, at least one of the components is immobilized on a solid substrate, from which the unbound components may be easily separated. The solid substrate can be made of a wide variety of materials and in a wide variety of shapes, e.g., microtiter plate, microbead, dipstick, resin particle, etc. The substrate preferably is chosen to maximize signal to noise ratios, primarily to minimize background binding, as well as for ease of separation and cost.

Separation may be effected for example, by removing a bead or dipstick from a reservoir, emptying or diluting a reservoir such as a microtiter plate well, rinsing a bead, particle, chromotograpic column or filter with a wash solution or solvent. The separation step preferably includes multiple rinses or washes. For example, when the solid substrate is a microtiter plate, the wells may be washed several times with a washing solution, which typically includes those components of the incubation mixture that do not participate in specific bindings such as salts, buffer, detergent, non-specific protein, etc. Where the solid substrate is a magnetic bead, the beads may be washed one or more times with a washing solution and isolated using a magnet.

Detection may be effected in any convenient way for cell-based assays such as two- or three-hybrid screens. The transcript resulting from a reporter gene transcription assay of the anti-cancer agent binding to a target molecule typically encodes a directly or indirectly detectable product, e.g., β-galactosidase activity, luciferase activity, and the like. For cell-free binding assays, one of the components usually comprises, or is coupled to, a detectable label. A wide variety of labels can be used, such as those that provide direct detection (e.g.,

radioactivity, luminescence, optical or electron density, etc). or indirect detection (e.g., epitope tag such as the FLAG epitope, enzyme tag such as horseseradish peroxidase, etc.). The label may be bound to an anti-cancer agent binding partner, or incorporated into the structure of the binding partner.

A variety of methods may be used to detect the label, depending on the nature of the label and other assay components. For example, the label may be detected while bound to the solid substrate or subsequent to separation from the solid substrate. Labels may be directly detected through optical or electron density, radioactive emissions, nonradiative energy transfers, etc. or indirectly detected with antibody conjugates, strepavidin-biotin conjugates, etc. Methods for detecting the labels are well known in the art.

The invention provides breast cancer gene-specific binding agents, methods of identifying and making such agents, and their use in diagnosis, therapy and pharmaceutical development. For example, breast cancer gene-specific pharmacological agents are useful in a variety of diagnostic and therapeutic applications as described herein. In general, the specificity of a breast cancer gene binding to a binding agent is shown by binding equilibrium constants. Targets which are capable of selectively binding a breast cancer gene preferably have binding equilibrium constants of at least about 10^7 M^{-1}, more preferably at least about 10^8 M^{-1}, and most preferably at least about 10^9 M^{-1}. The wide variety of cell based and cell free assays may be used to demonstrate breast cancer gene-specific binding. Cell-based assays include one, two and three hybrid screens, assays in which breast cancer gene-mediated transcription is inhibited or increased, etc. Cell-free assays include breast cancer gene-protein binding assays, immunoassays, etc. Other assays useful for screening agents which bind breast cancer polypeptides include fluorescence resonance energy transfer (FRET), and electrophoretic mobility shift analysis (EMSA).

In another aspect of the invention, pre- and post-treatment alterations in expression of two or more sets of breast cancer nucleic acid markers including, but not limited to, SEQ ID NOs:1-51 in breast cancer cells or tissues may be used to assess treatment parameters including, but not limited to: dosage, method of administration, timing of administration, and combination with other treatments as described herein.

Candidate pharmacological agents may include antisense oligonucleotides that selectively binds to a breast cancer nucleic acid marker molecule, as identified herein, to reduce the expression of the marker molecules in breast cancer cells and tissues. One of ordinary skill in the art can test of the effects of a reduction of expression of breast cancer

nucleic acid marker sequences *in vivo* or *in vitro*, to determine the efficacy of one or more antisense oligonucleotides.

As used herein, the term "antisense oligonucleotide" or "antisense" describes an oligonucleotide that is an oligoribonucleotide, oligodeoxyribonucleotide, modified oligoribonucleotide, or modified oligodeoxyribonucleotide which hybridizes under physiological conditions to DNA comprising a particular gene or to an mRNA transcript of that gene and, thereby, inhibits the transcription of that gene and/or the translation of that mRNA. The antisense molecules are designed so as to interfere with transcription or translation of a target gene upon hybridization with the target gene or transcript. Those skilled in the art will recognize that the exact length of the antisense oligonucleotide and its degree of complementarity with its target will depend upon the specific target selected, including the sequence of the target and the particular bases which comprise that sequence. It is preferred that the antisense oligonucleotide be constructed and arranged so as to bind selectively with the target under physiological conditions, i.e., to hybridize substantially more to the target sequence than to any other sequence in the target cell under physiological conditions.

Based upon the sequences of breast cancer expressed nucleic acids, or upon allelic or homologous genomic and/or cDNA sequences, one of skill in the art can easily choose and synthesize any of a number of appropriate antisense molecules for use in accordance with the present invention. In order to be sufficiently selective and potent for inhibition, such antisense oligonucleotides should comprise at least 10 and, more preferably, at least 15 consecutive bases that are complementary to the target, although in certain cases modified oligonucleotides as short as 7 bases in length have been used successfully as antisense oligonucleotides (Wagner et al., 1996). Most preferably, the antisense oligonucleotides comprise a complementary sequence of 20-30 bases. Although oligonucleotides may be chosen that are antisense to any region of the gene or mRNA transcripts, in preferred embodiments the antisense oligonucleotides correspond to N-terminal or 5' upstream sites such as translation initiation, transcription initiation or promoter sites. In addition, 3'-untranslated regions may be targeted. Targeting to mRNA splicing sites has also been used in the art but may be less preferred if alternative mRNA splicing occurs. In addition, the antisense is targeted, preferably, to sites in which mRNA secondary structure is not expected (see, e.g., Sainio et al., 1994) and at which proteins are not expected to bind. Finally, although the listed sequences are cDNA sequences, one of ordinary skill in the art may easily

derive the genomic DNA corresponding to the cDNA of a breast cancer expressed polypeptide. Thus, the present invention also provides for antisense oligonucleotides which are complementary to the genomic DNA corresponding to breast cancer expressed nucleic acids. Similarly, the use of antisense to allelic or homologous cDNAs and genomic DNAs are enabled without undue experimentation.

In one set of embodiments, the antisense oligonucleotides of the invention may be composed of "natural" deoxyribonucleotides, ribonucleotides, or any combination thereof. That is, the 5' end of one native nucleotide and the 3' end of another native nucleotide may be covalently linked, as in natural systems, via a phosphodiester internucleoside linkage. These oligonucleotides may be prepared by art-recognized methods, which may be carried out manually or by an automated synthesizer. They also may be produced recombinantly by vectors.

In preferred embodiments, however, the antisense oligonucleotides of the invention also may include "modified" oligonucleotides. That is, the oligonucleotides may be modified in a number of ways which do not prevent them from hybridizing to their target but which enhance their stability or targeting or which otherwise enhance their therapeutic effectiveness. The term "modified oligonucleotide" as used herein describes an oligonucleotide in which (1) at least two of its nucleotides are covalently linked via a synthetic internucleoside linkage (i.e., a linkage other than a phosphodiester linkage between the 5' end of one nucleotide and the 3' end of another nucleotide) and/or (2) a chemical group not normally associated with nucleic acids has been covalently attached to the oligonucleotide. Preferred synthetic internucleoside linkages are phosphorothioates, alkylphosphonates, phosphorodithioates, phosphate esters, alkylphosphonothioates, phosphoramidates, carbamates, carbonates, phosphate triesters, acetamidates, carboxymethyl esters, and peptides.

The term "modified oligonucleotide" also encompasses oligonucleotides with a covalently modified base and/or sugar. For example, modified oligonucleotides include oligonucleotides having backbone sugars that are covalently attached to low molecular weight organic groups other than a hydroxyl group at the 3' position and other than a phosphate group at the 5' position. Thus modified oligonucleotides may include a 2'-O-alkylated ribose group. In addition, modified oligonucleotides may include sugars such as arabinose instead of ribose. The present invention, thus, contemplates pharmaceutical preparations containing modified antisense molecules that are complementary to and

hybridizable with, under physiological conditions, breast cancer expressed nucleic acids, together with pharmaceutically acceptable carriers.

Antisense oligonucleotides may be administered as part of a pharmaceutical composition. Such a pharmaceutical composition may include the antisense oligonucleotides in combination with any standard physiologically and/or pharmaceutically acceptable carriers which are known in the art. The compositions should be sterile and contain a therapeutically effective amount of the antisense oligonucleotides in a unit of weight or volume suitable for administration to a patient. The term "pharmaceutically acceptable" means a non-toxic material that does not interfere with the effectiveness of the biological activity of the active ingredients. The term "physiologically acceptable" refers to a non-toxic material that is compatible with a biological system such as a cell, cell culture, tissue, or organism. The characteristics of the carrier will depend on the route of administration. Physiologically and pharmaceutically acceptable carriers include diluents, fillers, salts, buffers, stabilizers, solubilizers, and other materials, which are well known in the art.

Expression of breast cancer nucleic acid molecules can also be determined using protein measurement methods to determine expression of SEQ ID NOs:1-51, e.g., by determining the expression of polypeptides encoded by SEQ ID NOs:1-51 (SEQ ID NOs: 52-102, respectively). Preferred methods of specifically and quantitatively measuring proteins include, but are not limited to: mass spectroscopy-based methods such as surface enhanced laser desorption ionization (SELDI; e.g., Ciphergen ProteinChip System), non-mass spectroscopy-based methods, antibody-capture protein arrays and immunohistochemistry-based methods such as 2-dimensional gel electrophoresis.

SELDI methodology may be used, through procedures known to those of ordinary skill in the art, to vaporize microscopic amounts of tumor protein and to create a "fingerprint" of individual proteins, thereby allowing simultaneous measurement of the abundance of many proteins in a single sample. Preferably SELDI-based assays may be utilized to classify breast cancer tumors. Such assays preferably include, but are not limited to the following examples. Gene products discovered by RNA microarrays may be selectively measured by specific (antibody mediated) capture to the SELDI protein disc (e.g., selective SELDI). Gene products discovered by protein screening (e.g., with 2-D gels), may be resolved by "total protein SELDI" optimized to visualize those particular markers of interest from among SEQ ID NOs:1-51. Predictive models of tumor classification from SELDI measurement of multiple markers from among SEQ ID NOs:1-51 may be utilized for the SELDI strategies. In an

additional embodiment a set of primary lymph node-negative premenopausal breast cancer tissues may be preferably utilized to determine the risk classification of breast cancer based on SELDI results.

The invention also involves agents such as polypeptides that bind to breast cancer-associated polypeptides, i.e., SEQ ID NOs:52-102. Such binding agents can be used, for example, in screening assays to detect the presence or absence of breast cancer-associated polypeptides and complexes of breast cancer-associated polypeptides and their binding partners and in purification protocols to isolate breast cancer-associated polypeptides and complexes of breast cancer-associated polypeptides and their binding partners. Such agents also may be used to inhibit the native activity of the breast cancer-associated polypeptides, for example, by binding to such polypeptides.

The invention, therefore, embraces peptide binding agents which, for example, can be antibodies or fragments of antibodies having the ability to selectively bind to breast cancer-associated polypeptides. Antibodies include polyclonal and monoclonal antibodies, prepared according to conventional methodology.

Significantly, as is well-known in the art, only a small portion of an antibody molecule, the paratope, is involved in the binding of the antibody to its epitope (see, in general, Clark, W.R. (1986) The Experimental Foundations of Modern Immunology Wiley & Sons, Inc., New York; Roitt, I. (1991) Essential Immunology, 7th Ed., Blackwell Scientific Publications, Oxford). The pFc' and Fc regions, for example, are effectors of the complement cascade but are not involved in antigen binding. An antibody from which the pFc' region has been enzymatically cleaved, or which has been produced without the pFc' region, designated an $F(ab')_2$ fragment, retains both of the antigen binding sites of an intact antibody. Similarly, an antibody from which the Fc region has been enzymatically cleaved, or which has been produced without the Fc region, designated an Fab fragment, retains one of the antigen binding sites of an intact antibody molecule. Proceeding further, Fab fragments consist of a covalently bound antibody light chain and a portion of the antibody heavy chain denoted Fd. The Fd fragments are the major determinant of antibody specificity (a single Fd fragment may be associated with up to ten different light chains without altering antibody specificity) and Fd fragments retain epitope-binding ability in isolation.

Within the antigen-binding portion of an antibody, as is well-known in the art, there are complementarity determining regions (CDRs), which directly interact with the epitope of the antigen, and framework regions (FRs), which maintain the tertiary structure of the

paratope (see, in general, Clark, 1986; Roitt, 1991). In both the heavy chain Fd fragment and the light chain of IgG immunoglobulins, there are four framework regions (FR1 through FR4) separated respectively by three complementarity determining regions (CDR1 through CDR3). The CDRs, and in particular the CDR3 regions, and more particularly the heavy chain CDR3, are largely responsible for antibody specificity.

It is now well-established in the art that the non-CDR regions of a mammalian antibody may be replaced with similar regions of conspecific or heterospecific antibodies while retaining the epitopic specificity of the original antibody. This is most clearly manifested in the development and use of "humanized" antibodies in which non-human CDRs are covalently joined to human FR and/or Fc/pFc' regions to produce a functional antibody. See, e.g., U.S. patents 4,816,567, 5,225,539, 5,585,089, 5,693,762 and 5,859,205.

Fully human monoclonal antibodies also can be prepared by immunizing mice transgenic for large portions of human immunoglobulin heavy and light chain loci. Following immunization of these mice (e.g., XenoMouse (Abgenix), HuMAb mice (Medarex/GenPharm)), monoclonal antibodies can be prepared according to standard hybridoma technology. These monoclonal antibodies will have human immunoglobulin amino acid sequences and therefore will not provoke human anti-mouse antibody (HAMA) responses when administered to humans.

Thus, as will be apparent to one of ordinary skill in the art, the present invention also provides for $F(ab')_2$, Fab, Fv and Fd fragments; chimeric antibodies in which the Fc and/or FR and/or CDR1 and/or CDR2 and/or light chain CDR3 regions have been replaced by homologous human or non-human sequences; chimeric $F(ab')_2$ fragment antibodies in which the FR and/or CDR1 and/or CDR2 and/or light chain CDR3 regions have been replaced by homologous human or non-human sequences; chimeric Fab fragment antibodies in which the FR and/or CDR1 and/or CDR2 and/or light chain CDR3 regions have been replaced by homologous human or non-human sequences; and chimeric Fd fragment antibodies in which the FR and/or CDR1 and/or CDR2 regions have been replaced by homologous human or non-human sequences. The present invention also includes so-called single chain antibodies.

Thus, the invention involves polypeptides of numerous size and type that bind specifically to polypeptides selected from SEQ ID NOs:52-102, and complexes of both breast cancer-associated polypeptides and their binding partners. These polypeptides may be derived also from sources other than antibody technology. For example, such polypeptide binding agents can be provided by degenerate peptide libraries which can be readily prepared

in solution, in immobilized form or as phage display libraries. Combinatorial libraries also can be synthesized of peptides containing one or more amino acids. Libraries further can be synthesized of peptoids and non-peptide synthetic moieties.

Phage display can be particularly effective in identifying binding peptides useful according to the invention. Briefly, one prepares a phage library (using e.g. m13, fd, or lambda phage), displaying inserts from 4 to about 80 amino acid residues using conventional procedures. The inserts may represent, for example, a completely degenerate or biased array. One then can select phage-bearing inserts which bind to the breast cancer-associated polypeptide. This process can be repeated through several cycles of reselection of phage that bind to the breast cancer-associated polypeptide. Repeated rounds lead to enrichment of phage bearing particular sequences. DNA sequence analysis can be conducted to identify the sequences of the expressed polypeptides. The minimal linear portion of the sequence that binds to the breast cancer-associated polypeptide can be determined. One can repeat the procedure using a biased library containing inserts containing part or all of the minimal linear portion plus one or more additional degenerate residues upstream or downstream thereof. Yeast two-hybrid screening methods also may be used to identify polypeptides that bind to the breast cancer-associated polypeptides.

Thus, the breast cancer-associated polypeptides of the invention, including fragments thereof, can be used to screen peptide libraries, including phage display libraries, to identify and select peptide binding partners of the breast cancer-associated polypeptides of the invention. Such molecules can be used, as described, for screening assays, for purification protocols, for interfering directly with the functioning of breast cancer-associated polypeptides and for other purposes that will be apparent to those of ordinary skill in the art. For example, isolated breast cancer-associated polypeptides can be attached to a substrate (e.g., chromatographic media, such as polystyrene beads, a filter, or an array substrate), and then a solution suspected of containing the binding partner may be applied to the substrate. If a binding partner that can interact with breast cancer-associated polypeptides is present in the solution, then it will bind to the substrate-bound breast cancer-associated polypeptide. The binding partner then may be isolated.

As detailed herein, the foregoing antibodies and other binding molecules may be used for example, to identify tissues expressing protein or to purify protein. Antibodies also may be coupled to specific diagnostic labeling agents for imaging of cells and tissues that express breast cancer-associated polypeptides or to therapeutically useful agents according to

standard coupling procedures. Diagnostic agents include, but are not limited to, barium sulfate, iocetamic acid, iopanoic acid, ipodate calcium, diatrizoate sodium, diatrizoate meglumine, metrizamide, tyropanoate sodium and radiodiagnostics including positron emitters such as fluorine-18 and carbon-11, gamma emitters such as iodine-123, technitium-99m, iodine-131 and indium-111, nuclides for nuclear magnetic resonance such as fluorine and gadolinium.

The invention further includes protein microarrays for analyzing expression of breast cancer-associated peptides selected from SEQ ID NOs:52-102. In this aspect of the invention, standard techniques of microarray technology are utilized to assess expression of the breast cancer-associated polypeptides and/or identify biological constituents that bind such polypeptides. The constituents of biological samples include antibodies, lymphocytes (particularly T lymphocytes), and the like. Protein microarray technology, which is also known by other names including: protein chip technology and solid-phase protein array technology, is well known to those of ordinary skill in the art and is based on, but not limited to, obtaining an array of identified peptides or proteins on a fixed substrate, binding target molecules or biological constituents to the peptides, and evaluating such binding. See, e.g., G. MacBeath and S.L. Schreiber, "Printing Proteins as Microarrays for High-Throughput Function Determination," *Science* 289(5485):1760-1763, 2000.

Preferably antibodies or antigen binding fragments thereof that specifically bind polypeptides selected from the group consisting of SEQ ID NOs:52-102 are attached to the microarray substrate in accordance with standard attachment methods known in the art. These arrays can be used to quantify the expression of the polypeptides identified herein.

In some embodiments of the invention, one or more control peptide or protein molecules are attached to the substrate. Preferably, control peptide or protein molecules allow determination of factors such as peptide or protein quality and binding characteristics, reagent quality and effectiveness, hybridization success, and analysis thresholds and success.

The use of such methods to determine expression of breast cancer nucleic acids from among SEQ ID NOs:1-51 and/or proteins from among SEQ ID Nos:52-102 can be done with routine methods known to those of ordinary skill in the art and the expression determined by protein measurement methods may be correlated to MAI levels and used as a prognostic method for selecting treatment strategies for breast cancer patients.

Examples

Introduction

To establish a prognostic tool for designing breast cancer treatment regimens, expression patterns in primary breast cancer specimens were assessed and correlated with clinical outcome. Primary breast cancer tumors from premenopausal women with no lymph node metastases at the time of initial presentation were classified using the Mitotic Activity Index (MAI), which has been shown to predict disease-free survival in this type of disease. RNA was isolated, hybridized with Affymetrix HuFL human expression arrays, and analyzed to ascertain which genes discriminate the two groups.

Methods

Breast Cancers Used for RNA Microarray Expression Analysis

Primary frozen breast cancers from premenopausal women with no lymph node metastases at the time of initial presentation were assembled from material discarded following routine surgical removal for diagnostic purposes. Institutional review and human subjects approval for this project was obtained from Brigham and Women's Hospital. Fresh tissue was frozen in liquid nitrogen, and a single fragment split for confirmatory histology and RNA isolation. Individual fragments of frozen tumor tissues (estimated as 500 mg minimum) were split by fracturing under liquid nitrogen, and a portion processed for confirmatory histology using standard methods. The remaining tissue was used for synchronous RNA, protein, and DNA isolations with TRIzol reagents (Life Technologies, Inc., Rockville, MD) using standard methods. Only tumors where the actual frozen tissue contained >50% tumor cells were used.

Mitotic Activity Index

All tumors were classified by Mitotic Activity Index (Baak et al., 1989; van Diest et al., 1991; van Diest et al., 1992(a); Uyterlinde et al., 1990; van Diest et al., 1992(b); Jannink et al., 1996; Baak et al., 1992; Baak et al., 1993) using paraffin H&E stained tissues sections prepared for diagnostic purposes at the time of excision. The MAI is the total number of mitoses counted in 10 consecutive high-power fields (objective, x40; numeric aperture, 0.75; field diameter, 450 microns) in the most cellular area at the periphery of the tumor, with the subjectively highest mitotic activity (Jannink et al., 1995). Risk groups have previously been

defined using a threshold of 10 mitoses/unit area (Tosi et al., 1986; Jannink et al., 1995; Theissig et al., 1996). Tumors with MAI≥10 were assigned to the high risk group, and those with MAI≤3 to the low risk group.

Microarray Expression Analysis

RNA from 27 qualifying tumors was reverse transcribed and resultant cDNA used for *in vitro* transcriptional synthesis of fluorescently labeled nucleic acid probes which were then hybridized to Affymetrix HuFL human expression arrays (approximately 7100, probe sets, estimated 5800 unique genes). Hybridization images were analyzed with Affymetrix software to generate a data matrix of named probes by quantitative expression level in each tissue. RNA labeling, microarray hybridization, and microarray analysis were performed as per vendor's instructions for HuGeneFL array (Affymetrix, Santa Clara, CA). Four tumors were excluded from analysis because they failed to meet quality control criteria for microarray hybridization: 3 cases had low hybridization signal, one case had high background.

Results

Analysis of 23 primary breast cancer specimens from premenopausal lymph node negative women were split between two prognostic groups (Low MAI, MAI≤3, n=11 and High MAI, MAI≥10, n=12) and was accomplished as follows. Affymetrix HuFL expression values were normalized by scaling so the sum of AD (AD units are the quantitative expression units used by Affymetrix) values in each sample was 3,000,000; genes for which RNA abundance was absent or marginal were reset to a value of 0, then any values less than 20 were reset to 20. The result is the GPT datastate, which was then log transformed and discriminating genes selected by t-test comparison of the logged data between low and high MAI groups. Significance cutoffs for the t-tests used Permax <0.96 based on 10,000 random permutations of the data. Permax is a data analysis software tool for testing the significance of gene expression. It has been presented by Mutter, et al., 8th International Workshop on Chromosomes in Solid Tumors, Tucson, AZ, 2000; and is available online at biowww.dfci.harvard.edu/~gray/permax.html and from Robert J. Gray, Department of Biostatistical Science, Dana-Farber Cancer Institute, 44 Binney Street Boston, MA 02115. Permax details enclosed therein are incorporated by reference herein. Seventy eight of 7070 Affymetrix probe sets were selected by Permax.

Filters for minimum divergence between the average expression values of the two groups (Low vs. High MAI) were applied as follows: ratio of means ≥2, and difference between means ≥100. It was determined that 51/78 genes passed these filters. The final 51 selected genes which discriminate between low and high MAI subgroups appear in Table 1 and as SEQ ID NOs:1-51. Average expression in high MAI tumors and low MAI tumors is shown as HX and LX, respectively.

Table 1. Gene list identifying 51 genes that discriminate low from high MAI breast cancers.

SEQ ID NO	Short Name	GenBank Acc.No.	Permax	HX	LX	FOLDABS	DIFFABS
1	ABCB2	X57522	0.9577	501	83	6.0	417
2	ACTA2	X13839	0.7131	3098	6152	2.0	3054
3	AMD1	M21154	0.0808	257	50	5.1	207
4	APM2	D45370	0.3317	590	2682	4.5	2092
5	ASAH	U70063	0.8435	360	990	2.8	630
6	BARD1	U76638	0.5637	242	102	2.4	140
7	CCNH	U11791	0.9104	104	204	2.0	100
8	CCT2	U91327	0.8801	280	109	2.6	171
9	CDC20	U05340	0.0669	579	20	29.0	559
10	CDC34	L22005	0.6979	182	41	4.4	141
11	CDKN3	U02681	0.0072	454	63	7.2	391
12	CKS1	X54941	0.8823	539	219	2.5	320
13	CKS2	X54942	0.1881	413	119	3.5	294
14	COX7A1	M83186	0.9223	89	326	3.6	236
15	CPA3	M73720	0.8234	132	357	2.7	225
16	CPE	X51405	0.1984	80	243	3.0	163
17	CX3CR1	U20350	0.0317	70	328	4.7	258
18	DLG4	U83192	0.3427	20	179	8.9	159
19	DOC1	U53445	0.927	122	276	2.3	154
20	DXS9879E	X92896	0.9448	744	331	2.3	413
21	E2-EPF	M91670	0.9602	324	20	16.2	304
22	ElastinAlt2	U77846	0.8368	417	2210	5.3	1792
23	GTF2A1	U14193	0.7495	528	249	2.1	279
24	GUA5MPST	U10860	0.6129	599	114	5.2	485
25	H2AFX	X14850	0.8106	496	193	2.6	303
26	H2BFA	M60750	0.2334	508	143	3.6	365
27	Hevin	X86693	0.7484	529	1686	3.2	1157
28	HNRPH2	U01923	0.9056	106	231	2.2	126
29	HPV16E1Bind	U96131	0.2439	194	78	2.5	116
30	IDUA	M74715	0.1712	176	594	3.4	418
31	IGF1	X57025	0.9213	79	265	3.4	186
32	IQGAP2	U51903	0.9517	137	321	2.3	184
33	ISG15	M13755	0.9316	2133	386	5.5	1747
34	JAG1	U61276	0.9466	79	264	3.3	185
35	LAMA2	Z26653	0.8882	31	213	6.8	182
36	LAMB2	X79683	0.083	156	658	4.2	502
37	LBR	L25931	0.5991	221	68	3.2	153
38	MMP2	M55593	0.93	1765	3670	2.1	1905
39	MMSDH	M93405	0.9072	297	669	2.3	372
40	MYH11	AF001548	0.3109	164	777	4.7	612
41	MYLK	U48959	0.8351	158	680	4.3	522
42	PDE4A	L20965	0.8912	34	176	5.2	142
43	SCNN1A	X76180	0.694	352	864	2.5	511
44	SCYB10	X02530	0.4416	528	83	6.4	445
45	SNRPB	X17567	0.8965	1473	638	2.3	835
46	STAT1	M97936	0.9553	440	20	22.0	420
47	TAF2A	X07024	0.6819	193	65	2.9	127
48	TCEAL1	M99701	0.5595	241	749	3.1	508
49	TPM1	Z24727	0.5676	1266	2533	2.0	1267
50	TPS2	M33493	0.3638	194	892	4.6	698
51	UBCH10	U73379	0.1972	1519	639	2.4	880

Several features of selected genes provide reassurance that low frequency random events were not the cause of expression differences between groups. A review of the 51 selected genes (Table 1) shows that five pairs of genes known to be co-expressed were selected independently (two carboxypeptidases, two histones, two cdc28, two ubiquitins, two laminins, and myosin/tropomyosin), and reciprocal regulation of ligand and receptor, a common regulatory pattern, occurred once (laminin and lamin receptor) amongst genes selected.

The first expectation is that genes whose expression is linked to cell division would be represented in this comparison of tumors whose mitotic activity differs systematically. This was in fact the largest category of selected genes, with expression of 11/12 cell cycle genes greatest in the high MAI group. Genes which are preferentially expressed (at higher levels) in the low MAI group include those encoding extracellular matrix or enzymes which may remodel extracellular matrix (proteolytic enzymes).

The gene expression data presented in Table 1 can be used to generate an expression matrix of 51 selected genes by 23 tissues examined. Using standard clustering algorithms, dendrograms can be provided on the borders of the matrix (e.g., using Wards linkage and Euclidean distance) to show cluster relationships between tissues and genes. Similarly, a gene expression matrix can be generated using data normalized by standard deviation for each gene [STD(GPT)]. Dendrograms on borders of the matrix can be provided to show cluster relationships between tissues and genes. In this type of matrix, clustering of genes is based upon relative changes without bias due to absolute expression level, because each gene is expressed in standard deviation from the mean for that specific gene. However, unlike the other expression matrix described above, the absolute magnitude of expression cannot be directly inferred from this plot.

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The present invention is not limited in scope by the examples provided, since the examples are intended as illustrations of various aspects of the invention and other functionally equivalent embodiments are within the scope of the invention. Various modifications of the invention in addition to those shown are described herein will become apparent to those skilled in the art for the foregoing description and fall within the scope of the appended claims. The advantages and objects of the invention are not necessarily encompassed by each embodiment of the invention. All references, patents, and patent publications that are recited in this application are incorporated in their entirety herein by reference.

We claim:

Claims

1. A method for diagnosing breast cancer in a subject suspected of having breast cancer comprising:

obtaining from the subject a breast tissue sample suspected of being cancerous,

determining the expression of a set of nucleic acid molecules or expression products thereof in the breast tissue sample, wherein the set of nucleic acid molecules comprises at least two nucleic acid molecules selected from the group consisting of SEQ ID NOs:1-51.

2. The method of claim 1, wherein the set of nucleic acid molecules comprises at least 3 nucleic acid molecules selected from the group consisting of SEQ ID NOs:1-51.

3. The method of claim 1, wherein the set includes at least 4 nucleic acid molecules selected from the group consisting of SEQ ID NOs:1-51.

4. The method of claim 1, wherein the set includes at least 5 nucleic acid molecules selected from the group consisting of SEQ ID NOs:1-51.

5. The method of claim 1, wherein the set includes at least 10 nucleic acid molecules selected from the group consisting of SEQ ID NOs:1-51.

6. The method of claim 1, wherein the set includes at least 15 nucleic acid molecules selected from the group consisting of SEQ ID NOs:1-51.

7. The method of claim 1, wherein the set includes at least 20 nucleic acid molecules selected from the group consisting of SEQ ID NOs:1-51.

8. The method of claim 1, wherein the set includes at least 30 nucleic acid molecules selected from the group consisting of SEQ ID NOs:1-51.

9. The method of claim 1, wherein the set includes at least 40 nucleic acid molecules selected from the group consisting of SEQ ID NOs:1-51.

10. The method of claim 1, further comprising:

determining the expression of the set of nucleic acid molecules or expression products thereof in a non-cancerous breast tissue sample, and comparing the expression of the set of nucleic acid molecules or expression products thereof in the breast tissue sample suspected of being cancerous and the non-cancerous breast tissue sample.

11. A method for identifying a set of nucleic acid markers or expression products thereof effective for determining the prognosis of cancer, comprising:

obtaining a plurality of tumor tissue samples from a plurality of subjects afflicted with cancer,

classifying the plurality of tumor tissue samples according to mitotic activity index (MAI) into high MAI and low MAI groups,

determining differences in the expression of a plurality of nucleic acid molecules or expression products thereof in the tumor tissue samples, and

selecting as a set of nucleic acid markers the nucleic acid molecules or expression products thereof which are differentially expressed in the high MAI and the low MAI groups,

wherein the set of nucleic acid markers or expression products thereof effective for determining poor prognosis of cancer comprises one or more nucleic acid molecules or expression products thereof which are preferentially expressed in high MAI tumor tissue samples, and wherein the set of nucleic acid markers or expression products thereof effective for determining good prognosis of cancer comprises one or more nucleic acid molecules or expression products thereof which are preferentially expressed in low MAI tumor tissue samples.

12. The method of claim 11, wherein the cancer is breast cancer.

13. The method of claim 11, wherein the differences in the expression of a plurality of nucleic acid molecules are determined by a method selected from the group consisting of nucleic acid hybridization and nucleic acid amplification.

14. The method of claim 13, wherein the nucleic acid hybridization is performed using a solid-phase nucleic acid molecule array.

15. A method for selecting a course of treatment of a subject having or suspected of having cancer, comprising:

obtaining from the subject a tissue sample suspected of being cancerous,

determining the expression of a set of nucleic acid markers or expression products thereof which are differentially expressed in high MAI tumor tissue samples to determine the MAI of the tissue sample of the subject, and

selecting a course of treatment appropriate to the cancer of the subject.

16. The method of claim 15 wherein the cancer is breast cancer.

17. The method of claim 16, further comprising:

determining the expression of a set of nucleic acid markers that are differentially expressed in low MAI breast tumor tissue samples.

18. The method of claim 15, wherein the expression of a set of nucleic acid markers is determined by a method selected from the group consisting of nucleic acid hybridization and nucleic acid amplification.

19. The method of claim 18, wherein the nucleic acid hybridization is performed using a solid-phase nucleic acid molecule array.

20. A method for evaluating treatment of cancer, comprising:

obtaining a first determination of the expression of a set of nucleic acid molecules or expression products thereof, which are differentially expressed in high MAI tumor tissue samples to determine the MAI of the tissue sample from a subject undergoing treatment for cancer,

obtaining a second determination of the expression of a set of nucleic acid molecules or expression products thereof, which are differentially expressed in high MAI tumor tissue samples to determine the MAI of the second tissue sample from the subject after obtaining the first determination,

comparing the first determination of expression to the second determination of expression as an indication of evaluation of the treatment.

21. The method of claim 20, wherein the cancer is breast cancer.

22. The method of claim 21, further comprising:

determining the expression of a set of nucleic acid markers which are differentially expressed in low MAI breast tumor tissue samples.

23. The method of claim 20, wherein the expression of a set of nucleic acid markers is determined by a method selected from the group consisting of nucleic acid hybridization and nucleic acid amplification.

24. The method of claim 20, wherein the nucleic acid hybridization is performed using a solid-phase nucleic acid molecule array.

25. A solid-phase nucleic acid molecule array consisting essentially of at least two nucleic acid molecules selected from the group consisting of SEQ ID NOs:1-51 fixed to a solid substrate.

26. The solid-phase nucleic acid molecule array of claim 24, further comprising at least one control nucleic acid molecule.

27. The solid-phase nucleic acid molecule array of claim 24, wherein the set of nucleic acid molecules comprises at least 3 nucleic acid molecules selected from the group consisting of SEQ ID NOs:1-51.

28. The solid-phase nucleic acid molecule array of claim 24, wherein the set includes at least 4 nucleic acid molecules selected from the group consisting of SEQ ID NOs:1-51.

29. The solid-phase nucleic acid molecule array of claim 24, wherein the set includes at least 5 nucleic acid molecules selected from the group consisting of SEQ ID NOs:1-51.

30. The solid-phase nucleic acid molecule array of claim 24, wherein the set includes at least 10 nucleic acid molecules selected from the group consisting of SEQ ID NOs:1-51.

31. The solid-phase nucleic acid molecule array of claim 24, wherein the set includes at least 15 nucleic acid molecules selected from the group consisting of SEQ ID NOs:1-51.

32. The solid-phase nucleic acid molecule array of claim 24, wherein the set includes at least 20 nucleic acid molecules selected from the group consisting of SEQ ID NOs:1-51.

33. The solid-phase nucleic acid molecule array of claim 24, wherein the set includes at least 30 nucleic acid molecules selected from the group consisting of SEQ ID NOs:1-51.

34. The solid-phase nucleic acid molecule array of claim 24, wherein the set includes at least 40 nucleic acid molecules selected from the group consisting of SEQ ID NOs:1-51.

35. The solid-phase nucleic acid molecule array of claim 24, wherein the solid substrate comprises a material selected from the group consisting of glass, silica, aluminosilicates, borosilicates, metal oxides such as alumina and nickel oxide, various clays, nitrocellulose, and nylon.

36. The solid-phase nucleic acid molecule array of claim 24, wherein the nucleic acid molecules are fixed to the solid substrate by covalent bonding.

37. A solid-phase protein microarray comprising at least two antibodies or antigen-binding fragments thereof, that specifically bind at least two different polypeptides selected from the group consisting of SEQ ID NOs:52-102, fixed to a solid substrate.

38. The protein microarray of claim 37, wherein the microarray further comprises an antibody or antigen-binding fragment thereof, that binds specifically to a cancer-associated polypeptide other than those selected from the group consisting of SEQ ID NOs:52-102.

39. The protein microarray of claim 38, wherein the cancer-associated polypeptide other than those selected from the group consisting of SEQ ID NOs:52-102 is a breast cancer associated polypeptide.

40. The protein microarray of claim 37, further comprising at least one control polypeptide molecule.

41. The protein microarray of claim 37, wherein the antibodies are monoclonal or polyclonal antibodies.

42. The protein microarray of claim 37, wherein the antibodies are chimeric, human, or humanized antibodies.

43. The protein microarray of claim 37, wherein the antibodies are single chain antibodies.

44. The protein microarray of claim 37, wherein the antigen-binding fragments are $F(ab')_2$, Fab, Fd, or Fv fragments.

45. A method for identifying lead compounds for a pharmacological agent useful in the treatment of breast cancer, comprising:

contacting a breast cancer cell or tissue with a candidate pharmacological agent,

determining the expression of a set of nucleic acid molecules in the breast cancer cell or tissue sample under conditions which, in the absence of the candidate pharmacological agent, permit a first amount of expression of the set of nucleic acid molecules wherein the set of nucleic acid molecules comprises at least two nucleic acid molecules selected from the group consisting of SEQ ID NOs:1-51, and

detecting a test amount of the expression of the set of nucleic acid molecules, wherein a decrease in the test amount of expression in the presence of the candidate pharmacological agent relative to the first amount of expression indicates that the candidate pharmacological agent is a lead compound for a pharmacological agent which is useful in the treatment of breast cancer.

46. The method of claim 45, wherein the set of nucleic acid molecules is differentially expressed in high MAI breast tumor tissue samples.

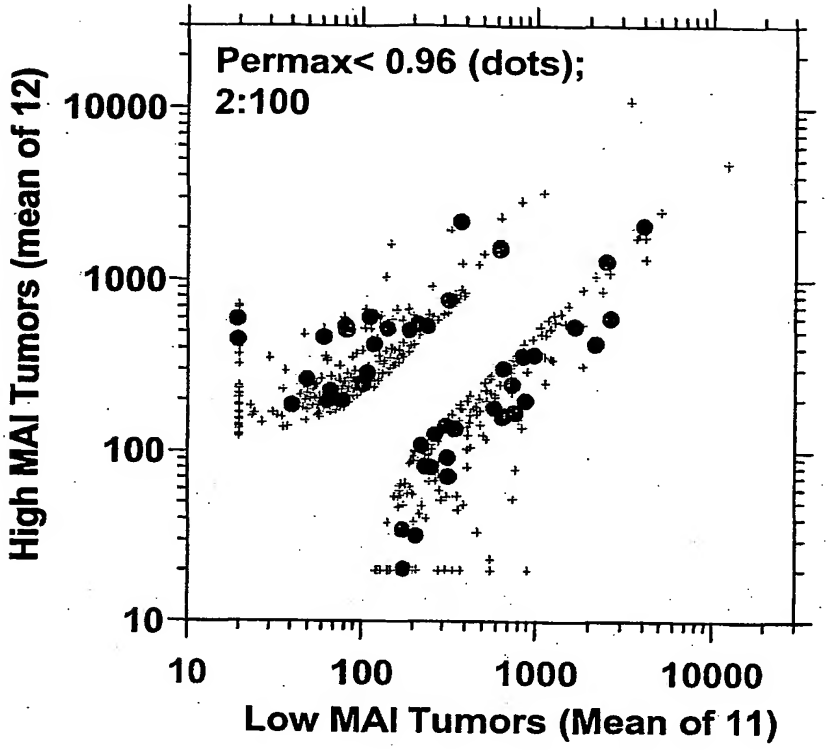
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Fig. 1

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